2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: E2006/lemborexant	Referring to Module 5 of the Dossier	
Name of Active Ingredient: lemborexant	Volume: Page:	

Study Title

A Long-Term Multicenter, Randomized, Double-Blind, Controlled, Parallel Group Study of the Safety and Efficacy of Lemborexant in Subjects With Insomnia Disorder

Investigator(s)/Site(s)

Mikko Kärppä, MD, PhD (principal investigator [PI]), et al.

Multicenter: 119 sites in North America (45), Europe (34), Asia (35), and Oceania (5) (refer to Appendix16.1.4 for the list of investigators and sites)

Publication (Reference)

None

Study Period

15 Nov 2016 (date of first subject's signed informed consent) to 31 May 2018 (Date of last subject's completion of the placebo-controlled portion of the study [Month 6 visit, end of Treatment Period 1])

Phase of Development

Phase 3

Objective(s)

Primary Objective

The primary objective was to determine the efficacy of lemborexant 5 mg (LEM5) and 10 mg (LEM10) compared to placebo (PBO) on subjective sleep onset latency (sSOL) after 6 months of treatment in subjects with insomnia disorder.

Secondary Objectives

Key Secondary Objectives:

- Determine the efficacy of LEM5 and LEM10 compared to PBO on subjective sleep efficiency (sSE) after 6 months of treatment in subjects with insomnia disorder
- Determine the efficacy of LEM5 and LEM10 compared to PBO on subjective wake after sleep onset (sWASO) after 6 months of treatment in subjects with insomnia disorder

Additional Secondary Objectives:

- Determine the efficacy of LEM5 and LEM10 compared to PBO on sSOL, sSE, sWASO, and subjective total sleep time (sTST):
  - for the first 7 nights of treatment
  - after 1 month of treatment
  - after 3 months of treatment
- Determine the efficacy of LEM5 and LEM10 compared to PBO on sTST at 6 months
- Evaluate the proportions of sleep onset and sleep maintenance responders to LEM5 and LEM10 compared to PBO as defined by response on sSOL or sWASO at 6 months and 12 months

- Evaluate the safety and tolerability of LEM5 and LEM10
- Evaluate the efficacy of LEM5 and LEM10 compared to PBO as measured by responses on the Insomnia Severity Index (ISI) and the Fatigue Severity Scale (FSS) after 6 months
- Evaluate rebound insomnia following discontinuation of treatment
- Evaluate morning sleepiness during and following completion of treatment
- Evaluate persistence of efficacy of LEM5 and LEM10 over 12 months

Exploratory Objectives

The following was to be explored for both LEM5 and LEM10 compared to PBO over Treatment Period 1 (Period 1) and over Treatment Period 2 (Period 2) with analyses dependent on whether subjects received active treatment or PBO during Period 1:

- Efficacy on quality of sleep
- Health outcomes on the EuroQOL version 5D-3L (EQ-5D-3L), Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH), and Patient Global Impression – Insomnia (PGI-Insomnia)
- Efficacy on sSOL, sSE, sWASO, sTST, ISI, and FSS
- Withdrawal symptoms after completion of treatment (Period 2 only)

The following was to be explored for LEM5 and LEM10:

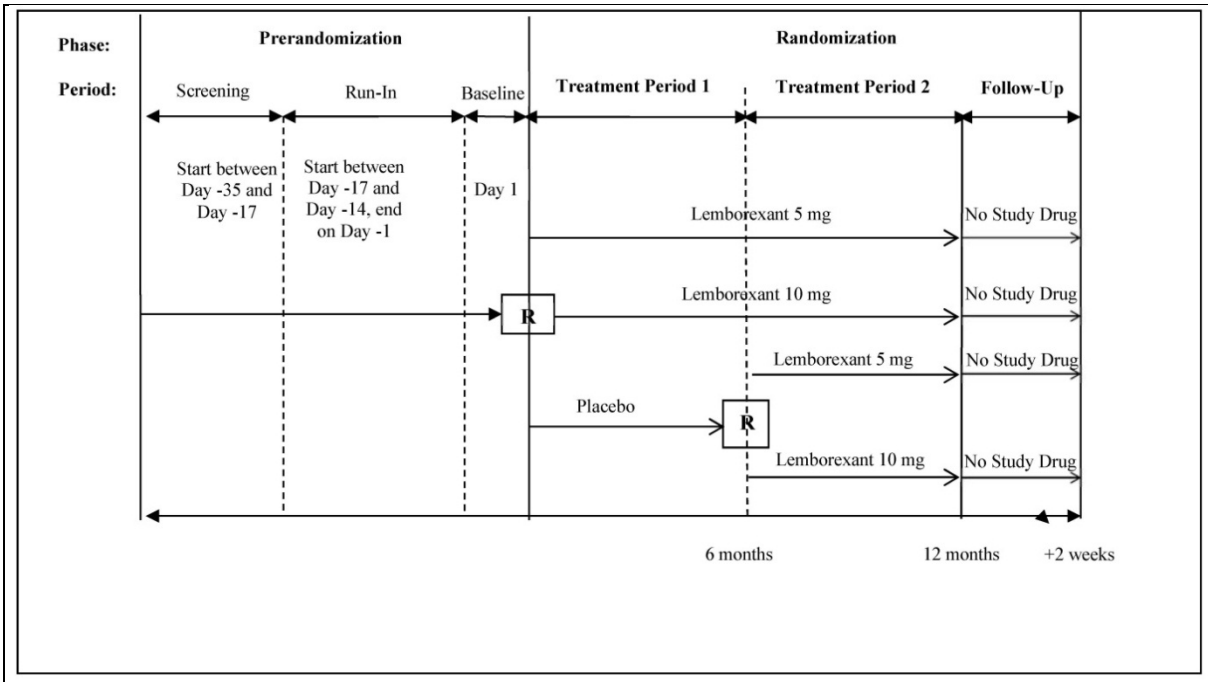
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- Population pharmacokinetic (PK) modeling for lemborexant
- PK/pharmacodynamic (PD) relationships between lemborexant concentrations and efficacy and safety variables

Methodology

This study (E2006-G000-303 [Study 303]) was a 12-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 2 dose levels of lemborexant in approximately 900 male or female subjects with insomnia disorder (subjects who complain of difficulties with sleep onset and/or sleep maintenance). Approximately 40% of the population was to be aged 65 years or older. This report was based on all available data for subjects up to and including the Month 6 visit (end of the placebo-controlled Period 1). The last Month 6 visit was 31 May 2018, at which time all remaining subjects had completed the placebo-controlled portion of the study.

The study had 2 phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase comprised 3 periods that lasted up to a maximum of 35 days: a Screening Period, a Run-in Period, and a Baseline Period. The Randomization Phase comprised a 6-month, placebo-controlled treatment period (Period 1). During the next 6 months (Period 2), subjects received only active treatment. Subjects were informed that they would all receive PBO at some point during the study and that all would receive active treatment for at least 6 months. They were not informed of either the timing of these periods or the timing of the second randomization. A 2-week Follow-Up Period then took place, followed by an End of Study (EOS) Visit.

Study design is presented below:



R = randomization

Number of Subjects (Planned and Enrolled)

Planned: Approximately 900 subjects with insomnia disorder (18 years or older) were randomized to receive double-blind LEM5 or LEM10 or PBO for 6 months.

Enrolled: A total of 2059 subjects signed informed consent for entry into the study. Of these, 1341 subjects continued into the Run-in Period, and 971 continued into the Treatment Period. A total of 646 subjects were randomized to the lemborexant treatment groups (323 subjects in LEM10 and 323 subjects in LEM5), while 325 subjects were randomized to the PBO treatment group.

Diagnosis and Main Criteria for Inclusion

Subjects were eligible for participation in the study if they met all of the following inclusion criteria:

1. Male or female, aged 18 years or older at the time of informed consent
2. Met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) criteria for Insomnia Disorder, as follows:
   - Complained of dissatisfaction with nighttime sleep in the form of difficulty getting to sleep, difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
   - Frequency of complaint ≥3 times per week
   - Duration of complaint ≥3 months
   - Associated with complaint of daytime impairment
3. At Screening: History of sSOL ≥30 minutes on at least 3 nights per week in the previous 4 weeks and/or sWASO ≥60 minutes on at least 3 nights per week in the previous 4 weeks
4. At Screening: Reported regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
5. At the first Screening Visit (Visit 1) and the second Screening Visit (Visit 2a): Reported regular bedtime, defined as the time the subject attempts to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject got out of bed for the day, between 05:00 and 10:00
6. At Screening and Study Baseline: ISI score ≥15
7. At the second Screening Visit (Visit 2a): Confirmation of current insomnia symptoms as determined from

responses on the Sleep Diary completed on at least 7 consecutive mornings (minimum 5 of 7 for eligibility), such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights

8. At the second Screening Visit (Visit 2a): Confirmation of regular bedtimes and waketimes, as determined from responses on the Sleep Diary completed on a minimum of 7 consecutive mornings between the first and the second screening visits, such that the subject had a regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours
9. At the second Screening Visit (Visit 2a): Confirmation of sufficient duration of time spent in bed, as determined from responses on the Sleep Diary completed on 7 mornings between the first and the second screening visits, such that there were not more than 2 nights with duration of time spent in bed <7 hours or >10 hours
10. At Baseline (Visit 3a): Reconfirmation of insomnia symptoms, as determined from responses on the Sleep Diary for the final 7 nights of the Run-in Period, such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights
11. At Baseline (Visit 3a): Confirmation of regular bedtimes and waketimes such that the subject had a regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours for the final 7 nights of the Run-In Period
12. At Baseline (Visit 3a): Reconfirmation of regular bedtime, defined as the time the subject attempted to sleep, between 21:00 and 01:00 and regular waketime, defined as the time the subject got out of bed for the day, between 05:00 and 10:00, for the final 7 nights of the Run-In period
13. Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
14. Willing to not start a behavioral or other treatment program for insomnia during the subject's participation in the study

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Test drug

Lemborexant 5 mg, lemborexant 10 mg, or lemborexant-matched placebo was taken orally in tablet form each night, immediately before the time the subject intended to try to sleep.

Run-in Period

All subjects received 1 lemborexant-matched placebo tablet during the Run-in Period.

Randomization Phase (Periods 1 and 2)

During Period 1 (Day 1 through end of Month 6), all subjects received 1 tablet per day as described below according to the treatment group to which the subject had been randomized:

- LEM5: 1 lemborexant 5 mg tablet (Batch/Lot number: 110254)
- LEM10: 1 lemborexant 10 mg tablet (Batch/Lot number: 110255)
- PBO: 1 lemborexant-matched placebo tablet (Batch/Lot number: 110252)

During Period 2 (Month 7 through 12), all subjects received 1 tablet per day as described below according to the treatment group to which the subject had been randomized:

- LEM5: 1 lemborexant 5 mg tablet (Batch/Lot number: 110254)
- LEM10: 1 lemborexant 10 mg tablet (Batch/Lot number: 110255)

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Not applicable.

Duration of Treatment

Run-in Period

All subjects were to receive 1 lemborexant-matched placebo tablet during the Run-in Period for at least 14 days between Days –17 and Day –1.

Randomization Phase (Periods 1 and 2)

All subjects were to receive 1 tablet per day according to the treatment group to which the subject was randomized (as described above).

Assessments

Efficacy

Electronic Sleep Diary

Subjects were to comply with requirements for completion of the Sleep Diary. Failure to comply required discussion with the medical monitor and could have resulted in discontinuation of the subject from the study.

The Sleep Diary was to be completed within an hour of morning waketime on each morning of the study from Screening through the end of the Follow-Up Period. This Sleep Diary yielded several self-reported measures of sleep that were used to determine eligibility, as well as to assess efficacy. In addition, the Sleep Diary included questions that related to morning sleepiness and to alcohol consumption.

Sleep Parameters:

- sSOL: estimated minutes from the time that the subject attempted to sleep until sleep onset
- sWASO: sum of estimated minutes of wake during the night after initial sleep onset until the time the subject stopped trying to sleep for the night, operationalized as the time the subject got out of bed for the day
- sTST: derived minutes of sleep from sleep onset until the time the subject stopped trying to sleep for the night
- sSE: proportion of sTST per subjective time spent in bed, calculated as the interval from the time the subject reports attempting to sleep until the time the subject stopped trying to sleep for the night (operationalized as the time the subject got out of bed for the day), and time spent asleep derived from subjective time spent in bed minus sWASO

Quality of Sleep:

The Sleep Diary was also used to assess the subject's global perception of quality of sleep on the previous night with the following question: "How would you rate the quality of your sleep last night?" Subjects rated the quality of their sleep on a scale from 1 to 9, with 1 being extremely poor and 9 being extremely good.

Morning Sleepiness:

The Sleep Diary was also used to assess subjective ratings of morning sleepiness with the following question: "How sleepy/alert do you feel this morning?" Subjects rated their sleepiness/alertness level on a scale from 1 to 9, with 1 being extremely poor (sleepy) and 9 being extremely good (alert).

Insomnia Severity Index

The ISI is a 7-item, self-report questionnaire assessing the nature, severity, and impact of insomnia (Bastien, et al., 2001). The dimensions evaluated were: severity of sleep onset; sleep maintenance; early morning awakening problems; sleep dissatisfaction; interference of sleep difficulties with daytime functioning; noticeability of the sleep problems by others; and distress caused by the sleep difficulties. A 5-point Likert scale was used to rate each item (from 0=no problem to 4=very severe problem) yielding a total score from 0 to 28. The total ISI score (items 1 to 7) was analyzed. In addition, items 4 to 7 (daytime functioning) were analyzed separately.

FSS

The FSS is a self-report scale on which subjects were instructed to choose a number from 1 to 7 that indicated their degree of agreement with each of 9 statements about their fatigue where "1" indicates strongly disagree and "7", strongly agree. The FSS total score was the sum of all responses to the 9 questions (Schwartz, et al., 1993). Higher total scores and average item scores indicate greater fatigue.

Pharmacokinetics

A single blood sample (4 mL per blood draw) was obtained at prespecified visits for plasma concentrations of lemborexant and its metabolites M4, M9, and M10. When these blood samples were obtained, the time of the 2 most recent doses administered before each sample was documented.

PK samples from all subjects who received active treatment were analyzed and reported in a standalone bioanalytical report.

Blood for determination of plasma concentrations of lemborexant and its metabolites were also to be drawn at the first report of a serious adverse event (SAE) or a severe unexpected AE and at its resolution. In this study, there were no SAEs that warranted a blood draw.

Pharmacodynamics

There were no assessments that were primarily PD. For purposes of PK/PD modeling, selected efficacy and safety assessments were to be used in lieu of PD assessments.

Pharmacogenomics

Not applicable.

Safety

Safety assessments consisted of monitoring and recording all AEs and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urinalysis; periodic measurement of vital signs, weight and ECGs; and the performance of physical examinations. At each clinic visit or phone call visit, subjects were inquired about whether a fall had occurred since the last visit. Safety was assessed at every clinic visit throughout the study, including after the last dose of study drug, and at the EOS, early termination (ET), EDD, and Unscheduled Visit.

Columbia-Suicide Severity Rating Scale

Suicidality was to be assessed using a self-rated electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) (Posner et al., 2011). The eC-SSRS assessed an individual's degree of suicidality, including both suicidal ideation and suicidal behavior. Qualified personnel were to evaluate positive responses on the eC-SSRS and were to take appropriate action as detailed in the training and certification process for administering the eC-SSRS.

Tyrer Benzodiazepine Withdrawal Symptom Questionnaire

An assessment of withdrawal symptoms was made using the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire (T-BWSQ) (Tyrer, et al., 1990) completed at the EOS Visit. Subjects were asked about the presence or absence and severity of the symptoms listed in the questionnaire. For each listed symptom, the subject was to respond "No" (Score = 0), "Yes – moderate" (Score = 1) or "Yes – severe" (Score = 2). The sum of responses was the subject's score.

Other Assessments

Health-Related Quality Life Assessments (EQ-5D-3L)

The EQ-5D-3L is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on quality of life and preferences/utility (Brooks, et al., 1996). The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a visual analogue scale from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

Patient Global Impression-Insomnia

The PGI-Insomnia is a self-report assessment asking about a subject's perception of the effects of the study drug on their sleep relative to their sleep before entering in the study. As such, the PGI-Insomnia did not have a Study Baseline and the outcome was not change from Study Baseline, but rather the global impression of the study drug's effects at the end of treatment. The PGI-Insomnia has 3 items related to study drug effects (a: helped/worsened sleep, b: decreased/increased time to fall asleep, and c: increased/decreased TST) and 1 item related to perceived appropriateness of study drug strength. The first 3 items were answered on a 3-point scale (1=positive medication effect, 2=neutral medication effect, 3=negative medication effect) and the last item on a different 3-point scale (medication: 1=too strong, 2=just right, 3=too weak). Each item was reported separately. This scale was used in studies of zolpidem (Roth, et al., 2006; Walsh, et al., 2008).

Work Productivity and Activity Impairment Questionnaire-General Health

The WPAI-GH collects data on absenteeism and presentism. The scale comprises 6 items that are used to create the 4 scores shown below. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (ie, worse outcomes).

- Percent work time missed due to health

- Percent impairment while working due to health
- Percent overall work impairment due to health
- Percent activity impairment due to health

Bioanalytical Methods

The handling and shipment of blood samples were described in the central laboratory manual provided to the study sites. Plasma concentrations of lemborexant and its metabolites M4, M9, and M10 were quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Statistical Methods

All statistical analyses were performed by the sponsor or designee after the database was locked and released for unblinding. The database lock was conducted after all subjects had completed Period 1 (Section 9.7.1.14); statistical analyses were performed using SAS (Version 9.4) software or other validated statistical software as required, on all available data up to and including the Month 6 visit in accordance with the statistical analysis plan (SAP). There was a second database lock when all subjects had completed at least half of Period 2 (through the visit at Month 9). A third (final) database lock will be conducted after the study is completed. Data from the second database lock are reported in the Synoptic CSR. Data from the third (final) database lock will be reported in the final CSR.

Primary and key secondary endpoints are discussed in this Core CSR, and other secondary and exploratory endpoints (only Period 1) are also discussed (Section 10 to 13). All statistical analyses are described in this section. Further details of the statistical analyses are included in the SAP (Appendix 16.1.9) which was finalized before database lock and treatment unblinding.

All descriptive statistics for continuous variables were reported using number of observations (n), mean (arithmetic unless otherwise specified), standard deviation (SD), median, minimum and maximum. Categorical variables were summarized as number and percentage of subjects. In summaries for safety the denominator for all percentages were the number of subjects in a given treatment group.

All statistical tests were based on the 5% level of significance (2-sided). If statistical comparisons were not defined, all pairwise comparisons were tested.

Study Endpoints

The following endpoints were analyzed for LEM5 and LEM10 compared to PBO. Where Sleep Diary endpoints were described, the time points refer to the mean of the final 7 nights before the visit unless otherwise stated.

Primary Endpoint:

The primary endpoint was the mean change from Study Baseline in sSOL at Month 6.

Secondary Endpoints:

Key Secondary Endpoints (all data are contained in this report)

- Mean change from Study Baseline in sSE at Month 6
- Mean change from Study Baseline of sWASO at Month 6

Additional Secondary Endpoints (only data through Month 6 are contained in this report)

- Mean change from Study Baseline of sSOL, of sSE, of sWASO, and of sTST, at the beginning of treatment (mean of the 7 nights after the first dose in Period 1), at Month 1 and at Month 3
- Mean change from Study Baseline of sTST at Month 6
- Proportion of responders at Month 6 and Month 12 (Synoptic Report only), where sleep onset responder was defined as follows: sSOL at Study Baseline was ≥30 minutes and mean sSOL at 6 months was ≤20 minutes, and sleep maintenance responder was defined as follows: sWASO at Study Baseline was ≥60 minutes and mean sWASO at 6 months was ≤60 minutes and showed a reduction of >10 minutes compared to Study Baseline.
- Change from Study Baseline in daytime functioning, assessed as the total score from the 4 items on daytime functioning, on the ISI, at Months 1, 3, and 6
- Change from Study Baseline on the FSS at Months 1, 3, and 6

- Ratings on the morning sleepiness item of the Sleep Diary, for:
  - The mean change from Study Baseline of the first 7 mornings after the first dose in Period 1 and Period 2
  - The mean change from Study Baseline at: Month 1, 3, and 6
  - The mean change from Study Baseline and from Period 2 Baseline (as appropriate): for subjects with 1, 3, 6, 9, and 12 months exposure (Synoptic Report only for subjects with 9 and 12 months exposure)
  - The mean change from Screening for the first 7 mornings and the second 7 mornings of the Follow-Up Period (Synoptic Report only)
- Rebound insomnia endpoints as assessed from the Sleep Diary during the Follow-Up Period (Synoptic Report only)
  - Change from Screening of sSOL on each of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-Up Period
  - Change from Screening of sWASO on each of the first 3 nights, mean sWASO of the first 7 nights and mean sWASO of the second 7 nights of the Follow-Up Period
  - Proportion of subjects whose sSOL is longer than at Screening for each of the first 3 nights, or whose mean sSOL is longer than at Screening for the first 7 nights or the second 7 nights of the Follow-Up Period
  - Proportion of subjects whose sWASO is higher than at Screening for each of the first 3 nights, or whose mean sWASO is higher than at Study Baseline for the first 7 nights or the second 7 nights of the Follow-Up Period
- Persistence of Effect
  - Mean change from Study Baseline of sSOL, of sSE, of sWASO and of sTST at Months 3, 6, 9, and 12 compared to Month 1
  - Mean change from Period 2 Baseline (Month 6) of sSOL, of sSE, of sWASO and of sTST at Months 9 and 12 compared to Month 7 (the first month of treatment in Period 2) (Synoptic Report only for subjects with 9 and 12 months exposure)
  - Mean change from Study Baseline and Period 2 Baseline (as appropriate) of sSOL, sSE, sWASO, and sTST at 3 and 6 months exposure compared to 1 month of exposure (Synoptic Report only for mean changes from Period 2 Baseline)
- Safety and Tolerability of Lemborexant
  - During Period 1, compared to PBO
  - For subjects exposed to lemborexant for 3, 6, 9, and 12 months (Synoptic Report only for subjects with 9 and 12 months exposure)

Exploratory Endpoints:

The following endpoints were also explored for LEM5 and LEM10. Except for PK endpoints, comparisons to PBO were made.

- Change from Study Baseline in the mean value of the item on quality of sleep from the Sleep Diary for:
  - The first 7 mornings after the first dose in Period 1
  - Months 1, 3, and 6
- Change from Study Baseline and Period 2 Baseline (as appropriate) in the mean value of the item on quality of sleep from the Sleep Diary for:
  - Subjects with 1, 3, 6, 9, and 12 months exposure (Synoptic Report only for subjects with 9 and 12 months exposure)
- Change from Study Baseline in:
  - EQ-5D-3L at Months 1, 3, and 6

  - WPAI-GH at Months 3 and 6
- Change from Study Baseline and Period 2 Baseline (as appropriate) in:
  - EQ-5D-3L for subjects with 3, 6, 9, and 12 months exposure to lemborexant (Synoptic Report only for subjects with 9 and 12 months exposure)
  - WPAI-GH for subjects with 3, 6, 9, and 12 months exposure to lemborexant (Synoptic Report only for subjects with 9 and 12 months exposure)
- Number and percentage of subjects with a rating of a positive medication effect on each PGI-Insomnia item (1) at Months 1, 3, and 6 (placebo-controlled Period 1), and (2) with 3, 6, 9, and 12 months exposure (Synoptic Report only for subjects with 9 and 12 months exposure)
- Change from Study Baseline and Period 2 Baseline (as appropriate) of sSOL, sSE, sWASO, sTST with 1, 3, 6, 9, and 12 months exposure, and ISI and FSS with 3, 6, 9, and 12 months exposure (Synoptic Report only for subjects with 9 and 12 months exposure)
- Mean score on the T-BWSQ of LEM5, and LEM10 compared to PBO at End of Study (Synoptic Report only)
- Plasma concentrations of lemborexant and its metabolites M4, M9, and M10
- PK of lemborexant using population modeling
- Relationships between lemborexant PK, efficacy, and/or safety variables using PK/PD modeling

Definitions of Analysis Sets

- The Safety Analysis Set was the group of subjects who received at least 1 dose of randomized study drug and had at least 1 postdose safety assessment.
- The On-Treatment Safety Analysis Set was the group of subjects who received at least 1 dose of lemborexant and had at least 1 post dose safety assessment (Synoptic Report only).
- The Full Analysis Set (FAS) was the group of randomized subjects who received at least 1 dose of randomized study drug and had at least 1 postdose primary efficacy measurement.
- The On-Treatment FAS was the group of subjects who received at least 1 dose of lemborexant and had at least 1 postdose primary efficacy measurement (Synoptic Report only).
- The 6-Month Completer Analysis Set was the group of subjects in the FAS who had all efficacy assessments up to and including Month 6 (ie, Week 1 and Months 1 to 6 visits) without missing primary or key secondary efficacy assessments at any of these visits.
- The PK Analysis Set was the group of subjects who had at least 1 quantifiable lemborexant plasma concentration or its metabolites, with adequately documented dosing history.
- The PK/PD Analysis Set was the group of subjects receiving either lemborexant or placebo who had efficacy or safety data with documented dosing history. In addition, subjects receiving lemborexant had at least 1 quantifiable lemborexant concentration data point as per the PK Analysis Set.
- The Per Protocol (PP) Analysis Set was the group of subjects who sufficiently complied with the protocol. This analysis set included all subjects in the Full Analysis Set who sufficiently complied with the protocol during Period 1.

Efficacy Analyses

Efficacy analyses for Period 1 were performed on the FAS unless otherwise specified. Different Study Baseline values were used for endpoints defined during Period 1 (ie, Day 1 to Month 6) and during Period 2 (ie, Month 7 to Month 12). Study Baseline values for each efficacy parameter were specified in Section 6.1.1 of the SAP (Appendix 16.1.9). The On-Treatment FAS was used for the on treatment summaries produced by time on treatment (Synoptic Report only).

Unless specified otherwise, all efficacy endpoints were derived by calculating the average of weekly (7 days) diary parameter values (Section 6.1 of the SAP).

12-month LEM exposure data were summarized by treatment (LEM5, LEM10) and duration of exposure in the Synoptic Report only (1 month, 3 months, 6 months, 9 months, and 12 months). Treatment groups were LEM5

and LEM10, and include both (a) LEM Period 1 subjects on the On-Treatment Full Analysis Set using the change from Study Baseline and (b) LEM Period 2 subjects previously receiving PBO on the On-Treatment Full Analysis Set using the change from Period 2 Baseline.

No hypothesis test was performed for efficacy endpoints beyond the Month 6 visit. Results of the primary and key secondary endpoints (for 6-month treatment during Period 1) were described in Section 11.4.1.1 and Section 11.4.1.2.1.

The primary and key secondary endpoints comparisons were tested following the gate-keeping testing procedure described in Section 3.3.3 of the SAP (see below) to control for the overall type I error at the 0.05 significance level. The first primary efficacy endpoint comparison was performed at the 0.05 significance level. The subsequent testing only proceeded if the previous test was statistically significant at the 0.05 level.

Primary Efficacy Analysis

The primary efficacy endpoint was the change from Study Baseline for sSOL at Month 6 of LEM10 and LEM5 compared to PBO.

Null Hypothesis: No difference exists in the mean change from Study Baseline to Month 6 of treatment with LEM10 (or LEM5) as compared with PBO.

Alternative Hypothesis: For sSOL, a difference exists in the mean change from Study Baseline to Month 6 for LEM10 (or LEM5) as compared with PBO.

The sSOL change from Study Baseline to Month 6 was analyzed using the mixed effect model repeated measurement (MMRM) analysis on the FAS. The model was adjusted for the corresponding Study Baseline value, region (North America, Europe and New Zealand, Asia), age group (<65 years old, ≥65 years old), treatment, time (the first 7 nights, Month 1, Month 2, Month 3, Month 4, Month 5, and Month 6), and the interaction of treatment by time. Since the sSOL is known to be non-normally distributed, a log transformation was used in the analysis.

The treatment comparison was performed using contrasts. The *P* value, least square (LS) means, and the 95% confidence interval (CI) for the treatment difference were also provided.

Secondary Efficacy Analysis

Key Secondary Efficacy Analyses

The change from Study Baseline of key secondary endpoints sSE and sWASO at Month 6 comparing LEM10 and LEM5 to PBO were analyzed as follows.

Change from Study Baseline of sSE at Month 6

The change from Study Baseline of sSE at Month 6 was analyzed using the MMRM analysis on the FAS. The model was adjusted for the corresponding Study Baseline value, region (North America, Europe and New Zealand, Asia), age group (<65 years old, ≥65 years old), treatment, time (the first 7 nights, Month 1, Month 2, Month 3, Month 4, Month 5, and Month 6) and the interaction of treatment by time.

The treatment comparison was performed using contrasts. The *P* value, LS means and the 95% confidence interval (CI) for the treatment difference were also provided.

Change from Study Baseline of sWASO on Month 6

The change from Study Baseline of sWASO on Month 6 was analyzed using the MMRM analysis on the FAS. The model was adjusted for the corresponding Study Baseline value, region (North America, Europe and New Zealand, Asia), age group (<65 years old, ≥65 years old), treatment, time (the first 7 nights, Month 1, Month 2, Month 3, Month 4, Month 5 and Month 6) and the interaction of treatment by time.

The treatment comparison was performed using contrasts. The *P* value, LS means and the 95% CI for the treatment difference were also provided.

Other Secondary Efficacy Analyses

For all other secondary endpoints described below, the continuous variable was summarized by using descriptive statistics by time point and the categorical variable were summarized as the number and percentage of subjects by time point.

Unless covered by the same model as the primary and secondary efficacy endpoints, or specified otherwise, the change from Study Baseline assessments were analyzed using MMRM assuming missing at random (MAR) (no missing value imputation) and the portion of responders was analyzed using the Cochran-Mantel-Haenszel

(CMH) test adjusted for region and age group. Missing values were considered as non-responders in all responder analyses. No multiplicity adjustment was made for all analyses.

The following endpoints were analyzed.

Efficacy Measures Derived from the Sleep Diary

- Change from Study Baseline of mean sSOL, mean sSE, mean sWASO and mean sTST for the first 7 nights, Months 1, 2, 3, 4 and 5; and mean sTST at Month 6; for LEM5 and LEM10 compared to PBO
- Change from Study Baseline and Period 2 Baseline of mean sSOL, mean sSE, mean sWASO and mean sTST for 1, 3, 6, 9 and 12 months exposure to LEM5 and LEM10. Data from subjects randomized to LEM5 or LEM10 at the start of the study used Study Baseline, data from subjects who were re-randomized to LEM5 or LEM10 in Period 2 used Period 2 Baseline. (Synoptic Report only for subjects with 9 and 12 months exposure)
- The proportion of responders, separately for sSOL and sWASO, was analyzed, for the first 7 nights, Months 1, 2, 3, 4, 5, and 6 for LEM5 and LEM10 compared to PBO:
  - A sleep onset responder was defined as: sSOL at Study Baseline was >30 minutes and mean sSOL at each month (the first 7 nights, Months 1, 2, 3, 4, 5, 6) was ≤ 20 minutes,
  - A sleep maintenance responder was defined as: sWASO at Study Baseline was >60 minutes and mean sWASO at each month (the first 7 nights, Months 1, 2, 3, 4, 5, 6) was ≤ 60 minutes and showed a reduction of >10 minutes compared to Study Baseline.

The proportion of responders was analyzed based on subjects with sSOL >30 minutes at Study Baseline for sSOL and subjects with sWASO >60 minutes at Study Baseline for sWASO.

- Morning sleepiness item of the Sleep Diary:
  - Change from Study Baseline of mean rating on morning sleepiness at the first 7 mornings after the first dose in Period 1, Month 1, Month 2, Month 3, Month 4, Month 5, and Month 6
  - Change of mean rating on morning sleepiness from Study Baseline and Period 2 Baseline for the first 7 mornings after the first LEM dose, 1, 3, 6, 9, and 12 months of exposure to LEM5 and LEM10. Data from subjects randomized to LEM5 or LEM10 at the start of the study used Study Baseline, data from subjects who were re-randomized to LEM5 or LEM10 in Period 2 used Period 2 Baseline. Change from Screening of mean rating on morning sleepiness of the first 7 mornings and the second 7 mornings in the Follow-Up Period (Synoptic Report only)
- Rebound insomnia endpoints during the Follow-Up Period as follows:
  - Change from Screening of sSOL on each of the first 3 nights, mean sSOL of the first 3 nights, mean sSOL of the first 7 nights, and mean sSOL of the second 7 nights of the Follow-Up Period (Synoptic Report only)
  - Change from Screening of sWASO on each of the first 3 nights, mean sWASO of the first 3 nights, mean sWASO of the first 7 nights and mean sWASO of the second 7 nights of the Follow-Up Period (Synoptic Report only)
  - Proportion of subjects whose sSOL was longer than at Screening by at least 5 minutes for each of the first 3 nights, mean sSOL of the first 3 nights, mean of the first 7 nights, and mean of the second 7 nights of the Follow-Up Period (Synoptic Report only)
  - Proportion of subjects whose sWASO was higher than at Screening by at least 5 minutes for each of the first 3 nights, mean sWASO of the first 3 nights, mean of the first 7 nights, and mean of the second 7 nights of the Follow-Up Period (Synoptic Report only)
- Analyses for persistence versus loss of effect were conducted for sSOL, sSE, sWASO, and sTST at Months 2 through 12 compared to Month 1. (Synoptic Report only)

Insomnia Severity Index and Fatigue Severity Scale

The following endpoints were analyzed for the ISI and FSS:

- Change from Study Baseline of the total score from items 1 to 7, and items 4 to 7, separately, on the ISI at

Months 1, 3, 6 of LEM5 and LEM10 compared to PBO

- Change from Study Baseline and Period 2 Baseline (as appropriate) of the total score from items 1 to 7, and items 4 to 7, separately, on the ISI for subjects with 3, 6, 9 and 12 months of exposure (Synoptic Report only)
- Change from Study Baseline on the FSS score at Months 1, 3, 6 of LEM5 and LEM10 compared to PBO
- Change from Study Baseline and Period 2 Baseline (as appropriate) on the FSS score for subjects with 3, 6, 9 and 12 months of exposure (Synoptic Report only)

The FSS was further analyzed to evaluate whether lemborexant treatment affected fatigue severity in those who entered the study with clinically significant levels of fatigue. These subgroup analyses included only those whose total FSS score was ≥18 at Study Baseline, which could be considered the lower threshold on the FSS for the presence of clinically significant fatigue. Analyses using the FSS analysis model were then applied. In addition, S-plot figures showed the proportion of subjects with varying rates of response on the FSS as follows:

- Cumulative proportion of subjects with varying absolute decreases from Study Baseline in total FSS score: The x-axis showed decrease from Study Baseline in 5-unit increments up to a ≥40-unit decrease from Study Baseline at Months 1, 3 and 6. Responder rates of –10 and –30 units were marked on the S-Plot.
- Cumulative proportion of subjects with varying relative decreases from Study Baseline in total FSS score: The x-axis showed decrease from Study Baseline in 10% increments up to a 100% decrease from Study Baseline at Months 1, 3 and 6. Responder rates of –10% and –30% were marked on the S-plot.

Pharmacokinetic Analyses

The plasma concentrations of lemborexant and its metabolites M4, M9, and M10 were summarized using descriptive statistics by dose, time and day based on the Safety Analysis Set.

A population PK approach was used to characterize the PK of lemborexant. For this approach, PK analysis data from this study was pooled with relevant data from Phase 1 and 2 studies, and other Phase 3 studies if available. The effect of covariates (eg, demographics, concomitant medications) on the PK of lemborexant was evaluated. The PK model was parameterized for oral clearance (CL/F) and volumes of distribution. Derived exposure parameters such as AUC and Cmax of lemborexant and any other relevant parameters were calculated from the model using the individual estimates parameterized for oral clearance and dosing history. A separate analysis plan for the population PK analyses was developed and finalized before the database lock.

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship between exposure to lemborexant and the efficacy variables including but not limited to sSOL, sSE, and sWASO, and the safety variables including but not limited to morning sleepiness and frequently occurring treatment-emergent adverse event (TEAEs), were explored graphically. Any emergent PK/PD relationships were evaluated by population PK/PD modeling. The population PK/PD analysis plan is described and results are reported in a separate document. Population PK and PK/PD analyses were performed using NONMEM Version 7.2 or later.

Safety Analyses

Evaluations of safety were performed on the relevant the Safety Analysis Set and the On-Treatment Safety Analysis Set (Synoptic Report only), as appropriate. All safety analyses were performed based on observed data using tabulation or descriptive statistics only.

No hypothesis testing was performed for safety analyses.

Other Analyses

<u>Health-Related Quality Life Assessments (EQ-5D-3L)</u>

The EQ-5D-3L instrument comprised questions on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale (EQ-VAS). Each dimension has 3 levels: no problem, some problems, extreme problems and the EQ-VAS is ranged from 0 (“Worst imaginable health state”) to 100 (“Best imaginable health state”).

Each dimension score was summarized separately at Study Baseline and each postbaseline time point (Month 1, Month 3, and Month 6) using frequency count on observed data only with no imputation. The change from Study Baseline of EQ-VAS was summarized by treatment group for Month 1, Month 3, and Month 6. The change from Study Baseline of EQ-VAS was analyzed using MMRM assuming MAR for Month 1, Month 3 and

Month 6 on observed data only based on FAS with no imputation for missing values.

The each dimension and EQ-VAS change from Study Baseline/Period 2 Baseline (as appropriate; Synoptic Report only) were summarized for the 12-month LEM exposure (On-Treatment Safety Analysis Set; Synoptic Report only), summarized by treatment group and duration of exposure.

Patient Global Impression-Insomnia

The PGI-Insomnia questionnaire captures the global impression of the study medication's effect at each postbaseline time point. The PGI-Insomnia has 3 items related to study medication effect (helped/worsened sleep, decreased/increased time to fall asleep, and increased/decreased TST) on a 3-point scale (1=positive medication effect, 2=neutral medication effect, and 3=negative medication effect) and 1 item related to perceived appropriateness of study mediation strength also on a 3-point scale (medication: 1=too strong, 2=just right, and 3=too weak).

Each item was summarized separately as number and percentage of subjects for each time point (Month 1, Month 3, and Month 6). Furthermore, each item was analyzed using chi-square test for Month 1, Month 3, and Month 6 on observed data only based on FAS with no imputation for missing values, and repeated for age subgroups. For this analysis, each item was categorized as follows: "positive medication effect" versus others for the first 3 item; "just right" versus others for the last item). This is also repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set; Synoptic Report only), summarized by treatment group and duration of exposure.

Work Productivity and Activity Impairment Questionnaire-General Health

The WPAI-GH consists of 6 questions: Q1=currently employed; Q 2=hours missed due to health problems; Q3=hours missed other reasons; Q4=hours actually worked; Q5=degree health affected productivity while working; Q6=degree health affected productivity in regular unpaid activities.

The four main outcomes derived by the following definition were summarized by visit. The change from Study Baseline for the main outcomes was summarized by visit. This is also repeated for the 12-month LEM exposure (On-Treatment Safety Analysis Set; Synoptic Report only), summarized by treatment group and duration of exposure.

Interim Analyses

Adjudication Committee

An independent Adjudication Committee was employed at intervals to review, in a blinded manner, AEs that could potentially have been considered cataplexy or seizure. A set of PTs constituting a customized Medical Dictionary for Regulatory Activities (MedDRA) query for cataplexy or seizure was used to identify events for adjudication (including cataplexy, muscle fatigue, muscular weakness, muscle tone disorder, hypotonia, drop attacks, slurred speech, diplopia, falls, convulsions [SMQ narrow and broad], atypical migraine, loss of consciousness, decreased consciousness, myoclonus, syncope, transient global amnesia, lipothymia [faintness] and transient ischemic attack). To assist in the preparation of narratives about such events and to support the committee's adjudication process, investigators and site staff were instructed to query subjects who reported any of the above events for supplemental information using a questionnaire for events potentially related to cataplexy and the SAE form for any of the above events considered serious.

Data Safety Monitoring Board (DSMB)

The DSMB served as an independent safety monitoring committee and performed the safety data reviews. The interim safety analyses were conducted by an independent statistician, who was working on behalf of Eisai from a Contract Research Organization (CRO) that was independent of study conduct. To maintain the credibility and integrity of the trial, procedures were implemented to ensure the DSMB and the independent statistician had sole access to the unblinded interim safety data until the planned analysis of the data. Full details of the DSMB operation procedures were documented in the DSMB charter. The sponsor was kept blinded until the unblinding of Period 1. No decision to stop the study based on superior efficacy or futility of lemborexant to placebo was planned.

Interim Analysis

No formal interim analysis was planned for this study.

Determination of Sample Size

The sample size was estimated for the comparison of LEM10 and LEM5 with PBO, with respect to the mean

change from Study Baseline at the end of Month 6 of the mean sSOL, the mean sSE and mean sWASO. This estimate was based on a sequential gate-keeping procedure at the 0.05 α-level in Section 3.3.3 of the SAP (Appendix 16.1.9). There was sufficient power for both the primary endpoint (sSOL) and key secondary endpoints (sSE and sWASO).

On the basis of dose-finding Study 201, across various lemborexant doses (1 to 25 mg) at Days 8 to 15, the standard deviation of change from Study Baseline for sSOL was assumed to be 33 minutes; for sSE was assumed to be 12%; and for sWASO was assumed to be 43 minutes. The LS mean treatment differences at Days 8 to 15 from Study 201 were as follows: for sSE 9.5% for LEM10 and 5.5%, for LEM5; for sWASO –26.6 minutes for LEM10, and –11.3 minutes for LEM5. As a result of the non-normal distribution of sSOL, the LS mean treatment difference is not available (geometric mean ratios were used). Therefore, estimating treatment difference using medians at Days 8 to 15 from Study 201, leads to a median treatment difference of approximately –6.8 minutes for LEM10. For LEM5, a median treatment difference was assumed approximately –13.2 minutes.

To detect a treatment difference in sSOL of at least –8.7 minutes, a sample size of 300 per treatment group at 5% (2-sided) level of significance had >90% power for comparing a dose of lemborexant with PBO.

To detect a treatment difference in sSE of at least 5.5%, a sample size of 300 per treatment group at 5% (2-sided) level of significance had >99% power for comparing a dose of lemborexant with PBO.

For sWASO, a total of 900 subjects (300 per treatment group) had 90% power to detect a difference of –11.4 minutes for LEM5 and LEM10 compared to PBO (see Table 7 in Section 9.7.2).

The study also had adequate power for the secondary analysis of responders. A sleep onset responder was defined as follows: sSOL at Study Baseline was ≥30 minutes and mean sSOL at 6 months was ≤20 minutes, and a sleep maintenance responder was defined as follows: sWASO at Study Baseline was ≥60 minutes and mean sWASO at 6 months was ≤60 minutes and showed a reduction of >10 minutes compared to Study Baseline. A total of 900 subjects gave >99% power to detect a treatment difference in sleep onset responder rates of 16% and sleep maintenance responder rates of 24.4%, both compared with placebo.

The above sample size also met regulatory safety requirements. Even with early discontinuation rates as high as 50% at Month 6 (ie, 150 subjects remaining) and 60% by Month 12 (ie, 120 subjects remaining in each treatment group), the requirement for 100 subjects in each of the elderly and non-elderly age-groups to complete 12-months of treatment on 5 or 10 mg lemborexant would be met. In addition, a total of at least 420 subjects would complete 6 months of treatment with 5 or 10 mg lemborexant.

Results

Subject Disposition/Analysis Sets

A total of 646 subjects were randomized to the lemborexant treatment groups (323 subjects to LEM10 and 323 subjects to LEM5), while 325 subjects were randomized to PBO. Twelve of the randomized subjects (4 subjects in each of the LEM10, LEM5, and PBO treatment groups) were not treated with study drug. The majority of subjects in all treatment groups completed Period 1 (70.8%, 78.7%, and 80.1% of subjects in the LEM10, LEM5, and PBO treatment groups, respectively).

The FAS included 949 subjects (315, 316, and 318 subjects in the LEM10, LEM5, and PBO treatment groups, respectively) and the Safety Analysis Set included 947 subjects (314, 314, and 319 subjects in the LEM10, LEM5, and PBO treatment groups, respectively).

Efficacy

Electronic Sleep Diary Endpoints for Lemborexant Versus Placebo

- There were statistically significantly greater decreases from Study Baseline in sSOL at Month 6 for both doses of lemborexant (LEM10 and LEM5) compared to PBO, indicating that subjects reported improvement of time to sleep onset at the end of 6 months of treatment.
- There were statistically significantly greater increases from Study Baseline in sSE, and statistically significantly greater decreases from Study Baseline in sWASO at Month 6 for both doses of lemborexant compared to PBO, indicating that subjects reported improvement in sleep maintenance at the end of 6 months of treatment.
- Statistically significant treatment differences in change from Study Baseline were also demonstrated for

sSOL, sSE, and sWASO after the first 7 nights, and at Month 3 (all indicating a positive outcome), and for sSOL and sSE also at Month 1 for both doses of lemborexant compared to placebo.

- There were statistically significantly greater increases from Study Baseline in sTST over the first 7 nights and at Months 1, 3, and 6 for both doses of lemborexant compared to PBO, indicating that subjects reported more time spent asleep at the end of 6 months of treatment.

Persistence of Effect

- The larger positive effect on both sleep onset and sleep maintenance parameters with both doses at Months 3 and 6 compared to Month 1 demonstrated that the effect persisted over time.

Responder Analyses

- Sleep Onset Responders: There was a statistically significantly higher proportion of sleep onset responders on sSOL for both doses of lemborexant compared to PBO at the end of 6 months of treatment.
- Sleep Maintenance Responders: There was a statistically significantly higher proportion of sleep maintenance responders on sWASO for both doses of lemborexant compared to PBO at the end of 6 months of treatment.

Other Efficacy Analyses

- There were statistically significantly greater decreases from Study Baseline in both total ISI score and scores on the Daytime Functioning items on the ISI at the end of 6 months of treatment for both doses of lemborexant compared to PBO.
- There were statistically significantly greater decreases from Study Baseline in both average FSS scores and total sum FSS scores at the end of 6 months of treatment for both doses of lemborexant compared to PBO.
- Subgroup analyses of sSOL, sWASO and sSE showed that the efficacy of lemborexant was similar across age and sex subgroups. Both for subjects age <65 years and ≥65 years, and both for males and females, these changes from Study Baseline in sSOL, sWASO, and sSE at the end of 6 months of treatment were statistically significantly different (better) for both doses of lemborexant compared to PBO.

Exploratory Efficacy Variables

- The mean ratings on the quality of sleep question from the sleep diary were statistically significantly higher for both doses of lemborexant compared to PBO at the end of 6 months of treatment, indicating greater improvement.
- The mean change from Study Baseline of EQ-5D-3L VAS scores were numerically higher (better) for LEM10 and LEM5 compared to PBO at the end of 6 months of treatment, indicating greater improvement of patient reported health state.
- For the PGI-Insomnia, there was a statistically significantly greater improvement for helped subjects to sleep, reduced time to fall asleep, and increased sTST, for both doses of lemborexant compared to PBO at the end of 6 months of treatment. For both doses at the end of 6 months of treatment, the proportion of subjects who selected that the treatment strength was "just right," was higher compared to subjects in the PBO treatment group (statistically significant for LEM10).
- For the WPAI-GH at the end of 6 months of treatment, the responses to all productivity questions indicated a numerically better outcome for LEM10 and LEM5 compared to PBO.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

Plasma concentrations of lemborexant and its metabolites (M4, M9 and M10) are summarized for the Safety Analysis Set in Table 14.2.2.1 and provided by subject for the Safety Analysis Set in Listing 16.2.6.8.

The concentrations of lemborexant and its metabolites following multiple-dose administration are in the range of plasma concentrations in subjects from another study (E2006-A001-002 [Study 002]) in which 5 or 10 mg multiple-dose lemborexant was administered.

The standalone report for PK/PD also details lemborexant PK parameters used in exposure-response analyses.

Population PK and PK/PD analyses integrating data from Study E2006-G000-304 (Study 304) and Study 303 will be summarized in a separate standalone report.

Safety

- During Period 1, in general, TEAEs were reported for a similar proportion of subjects in the LEM10, LEM5 and PBO treatment groups (59.6% for LEM10, 61.1% for LEM5, and 62.7% for PBO).
- The majority of TEAEs in all treatment groups were of mild or moderate severity, with severe TEAEs reported for a small number of subjects in each treatment group (2.5% for LEM10, 4.1% for LEM5, and 3.1% for PBO).
- Common TEAEs (reported for ≥2% of subjects in any lemborexant treatment group) reported during Period 1 were somnolence (13.1%, 8.6%, 1.6% subjects in the LEM10, LEM5, and PBO treatment groups respectively), nasopharyngitis (9.2%, 9.6%, 12.5%), headache (6.7%, 8.9%, 6.6%), influenza (5.1%, 4.8%, 4.7%), upper respiratory tract infection (3.5%, 4.1%, 3.1%), fatigue (3.5%, 3.8%, 0.3%), back pain (2.9%, 3.8%, 2.5%), urinary tract infection (2.9%, 1.3%, 2.2%), gastroenteritis (2.2%, 1.6%, 1.3%), nightmare (2.2%, 1.3%, 0.3%), nausea (1.3%, 2.5%, 0.9%), abnormal dreams (1.3%, 2.2%, 1.9%), and arthralgia (1.0%, 4.5%, 2.8%).
- Overall, treatment-related TEAEs were reported for a higher proportion of subjects in the LEM10 and LEM5 treatment groups (29.0% and 24.8% subjects, respectively) when compared to the PBO treatment group (13.8% subjects). The most commonly reported treatment-related TEAE was somnolence, reported for 12.7%, 8.6%, and 1.3% subjects in the LEM10, LEM5, and PBO treatment groups, respectively.
- There were no deaths reported during Period 1. Overall, treatment-emergent SAEs were reported for 2.9% of subjects in the LEM10 treatment group, 2.2% of subjects in the LEM5 treatment group, and 1.6% of subjects in the PBO treatment group. Only one treatment-emergent treatment-related SAE (disturbance in attention) was reported (LEM10 treatment group), with none in the LEM5 and PBO treatment groups.
- Overall, the incidence of TEAEs leading to discontinuation of study drug reported during Period 1 was higher in the LEM10 compared to LEM5, and PBO treatment groups (8.3%, 4.1%, and 3.8% subjects, respectively). TEAEs leading to discontinuation of study drug (reported for ≥2 subjects in any lemborexant treatment group) included somnolence (2.9%, 1.0% of subjects in the LEM10 and LEM5 treatment groups, respectively), nightmare (1.3%, 0.3%), and palpitations (0.6%, 0). These events were treatment-related.
- Overall, TEAEs that were defined as cataplexy or potential cataplexy were reported for 3.2%, 2.9%, and 3.1% subjects in the LEM10, LEM5, and PBO treatment groups, respectively. Fall was reported for 1.6%, 1.6%, and 3.1% subjects in the LEM10, LEM5, and PBO treatment groups, respectively. No TEAE of seizure was reported in any treatment group.
- The overall incidence of potential abuse-related TEAEs in LEM10 and LEM5 was numerically higher than for PBO during Period 1. The potential abuse-liability event of somnolence was reported for 13.1% subjects in the LEM10 treatment group, 8.6% subjects in the LEM5 treatment group, and 1.6% subjects in the PBO treatment group. Therefore, the difference among treatment groups can be explained in part by the above somnolence TEAEs.
- Overall, there were no clinically significant findings for clinical laboratory tests, vital signs, weight or ECGs.
- The rating for the morning sleepiness indicated statistically significantly more improvement for LEM10 and LEM5 compared to PBO over the first 7 nights (LEM10 and LEM5), and at Month 3 (LEM10), and Month 6 (LEM10) of Period 1.
- Lemborexant was generally well tolerated in the study population.

Conclusions

- Both doses of lemborexant demonstrated statistically significantly larger changes (positive outcome) from Study Baseline compared to placebo for both sleep onset and sleep maintenance variables after 6 months of treatment. Statistically significant treatment differences in change from Study Baseline were also demonstrated for sSOL, sSE, and sWASO after 7 nights, and at Month 3 (all indicating a positive outcome), and for sSOL and sSE also at Month 1 for both doses of lemborexant compared to placebo.
- Lemborexant was generally well tolerated at both doses studied, LEM5 and LEM10.

Date of Report

04 Dec 2018